Reply to Jensen and Blackledge: Dual quantifications of intrinsically disordered proteins by NMR ensembles and molecular dynamics simulations

Jensen and Blackledge (1) compared the residual dipolar couplings (RDCs) of the molecular recognition element of the C-terminal domain of the measles virus nucleoprotein (NTAIL) computed from the NMR-based ensembles and the ones computed from the ensemble of our molecular dynamics (MD) simulations (2). They found that the NMR-based ensemble led to better consistency with experimental RDCs than the MD ensemble. However, the MD ensemble did reproduce well the experimental secondary chemical shifts (Cs). They speculated that this may possibly arise from the fact that RDCs are more sensitive to orientational order of local helical structures than Cs. On the basis of this sensitivity, they conclude that RDCs can be used to precisely characterize intrinsically disordered proteins (IDPs).

We would like to emphasize here that this does not mean that the NMR-based ensemble method is superior to MD simulation to study IDPs. To obtain a global characterization of an IDP, it is of great help to quantify its underlying energy landscape. Such a landscape can be characterized by several key features, including local ones, such as basins and their depths (metastable substates and their corresponding populations), as well as the global topography such as the relative positions of basins and the barrier heights between them (related to kinetics and mechanisms). The NMR-based ensemble method may provide useful local information around basins, but less on the global interbasin crossing. Thus, from this perspective, MD modeling plays an irreplaceable role in obtaining a global and quantitative understanding of IDPs as clearly shown in our binding-folding studies (2).

In practice, the successful application of MD modeling on IDPs is dependent on two factors: force field and sampling. The former determines the accuracy, whereas the latter limits the convergence and ergodicity. The force field we used is the recently developed CHARMM22* (3). The simulation time in our physics-based simulation with explicit solvent represents an average level of computer power among most of the research groups. However, it is worth mentioning that even with specially designed computers (3) or with significantly increased computational power, it is still challenging with these types of experiments to obtain a complete sampling for a quantitative comparison with extremely local sensitivity. Importantly, as the authors claimed (3), “the major discrepancy with experiments appears to be that the unfolded state is slightly too collapsed, suggesting an area for further force field improvements.” This indicates that we still need to further improve both force field and sampling in MD modeling to reach results more quantitatively consistent with experiments.

Besides focusing on improvement of force field and sampling, there is another feasible way to improve the ensemble prediction. That is to integrate experimental data, especially from NMR, into MD simulation (4). Considering that the ensembles guessed from the experimental data are often with potential risks, such as probe’s interference, overfitting, and non-uniqueness, we believe that neither NMR nor MD alone at present can provide a full quantitative picture of IDPs. These two approaches are complementary. The field should benefit greatly from their combination or from multiscale strategies.

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